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Familial Myelodysplastic Syndrome With Early Age of Onset

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A family is described in which three members, the propositus, his brother, and son, developed a myelodysplastic syndrome (MDS) at the ages of 52, 35, and 25, respectively. A fourth member, the paternal uncle of the propositus, was diagnosed with chronic lymphocytic leukemia. Two of the three affected individuals had megaloblastoid marrows with recognizable bone marrow cytogenetic abnormalities and progressive, nonleukemic bone marrow failure. The propositus was unresponsive to G-CSF and eventually died of sepsis. The second affected family member died of bone marrow transplant complications. The third affected family member underwent bone marrow transplantation and is showing signs of graft survival despite minor complications. The affected members of this pedigree appear to represent a continuum in severity of disease and, therefore, pathogenesis. The pattern of inheritance and clinical progression of the disease suggest a genetic defect which may predispose individuals to the development of MDS. Am. J. Hematol. 64:53–58, 2000. © 2000 Wiley-Liss, Inc.

Key words: myelodysplastic syndrome; familial; bone marrow

INTRODUCTION

Myelodysplastic syndromes (MDS) are a diverse group of diseases often accompanied by well-characterized chromosomal changes and a predilection for progression to acute leukemias of non-lymphocytic origin [1,2]. It has been reported that first-degree relatives of patients with MDS have a higher than expected incidence of the disorder [3], although few have described a familial myelodysplastic syndrome as such [4–7].

Acquired MDS generally occurs in elderly patients with a median age of 65–70 years [8–17]. MDS rarely occurs in children or younger adults; in one study only 6.7% of de novo cases occurred in patients 50 years of age or less [18]. These patients are of great clinical significance as their prognosis is generally poorer although, paradoxically, they are more amenable to intensive therapeutic approaches such as allogeneic bone marrow transplantation (BMT).

We present a rare combination of familial MDS and age of onset before 55, with three and possibly four affected members in the pedigree.

CASE REPORTS

A family tree is shown in Figure 1.

Propositus (II-6)

In September 1991, a 52-year-old Caucasian male was admitted to hospital after a 1-month history of symptoms of anemia and ease of bruising. Pancytopenia was apparent with Hb 75 g/L (normal range 140–180 g/L), MCV 98.8 fL (80–94 fL), absolute neutrophil count (ANC) 0.7 $\times 10^9$/L ((2.0–7.5) $\times 10^9$/L), and platelets 71 $\times 10^9$/L ((150–450) $\times 10^9$/L). Serum B_{12} and folate levels were normal, and Ham's test was negative. He had no hepatosplenomegaly or lymphadenopathy and physical exam was otherwise unremarkable. The patient had been employed with the Canadian Armed Forces for over 30 years as a vehicle technician and had an unknown exposure profile to benzene and other chemicals. There was no history of chemotherapy or smoking. A bone marrow aspirate was hypercellular due to a marked degree of erythroid hyperplasia with moderately pronounced dys-

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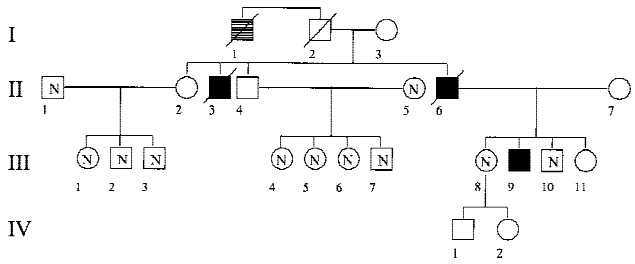

Fig. 1. Pedigree of family affected with MDS. The black and shaded symbols represent individuals diagnosed with MDS and CLL with possible dysplastic features, respectively. Deceased individuals are indicated with a slash. N indicates that a full blood count was performed and was normal. A blood count was not done on those unaffected individuals not marked with N.

erythropoietic changes. Granulopoiesis and thrombopoiesis were reduced with mild dysplastic changes. Nonerythroid blasts were 12% with no differentiation and no reactivity to either PAS or myeloperoxidase. More mature erythroid precursors were positive for PAS in a diffuse to focal pattern. Bone marrow biopsy showed a markedly hypercellular marrow with a fat to cell ratio of 20/80. There was an atypical infiltrate consisting of dysplastic erythroid precursors. A diagnosis of MDS, refractory anemia and excess blasts (RAEB), was made. Cytogenetic analysis revealed that only two out of 30 cells examined had a normal karyotype. The model karyotype was 44,XY, del(5)(q11.1), −7, der(15)t(5;15)(q11.1; q11.1) − 18 [28]/46,XY [2] with the abnormal clones consistently showing (1) monosomy 7, (2) monosomy 15, (3) monosomy 18, and (4) a break in the centromeric region of chromosome 5 with gain of 5p and 5q markers.

Over the next few months the patient was supported with packed red cell and platelet transfusions with increasing frequency and treated empirically for episodes of febrile neutropenia as an inpatient. No foci of infection were ever isolated. An open biopsy of a bone scan-positive navicular lesion showed no evidence of bacterial infection. G-CSF was tried on two occasions for up to a one week period with no significant increase in neutrophil counts. The patient recovered his white cell counts spontaneously and remained clinically well as an outpatient.

In April 1992 he was admitted to hospital with chest pain and shortness of breath. His Hb was 93 g/L, ANC 0.15×10^9/L, neutrophils 0.3×10^9/L, and platelets 10×10^9/L. Clinical exam and investigations revealed a nontamponading pericardial effusion not requiring intervention. The patient went on to develop a left lower lobe infiltrate and bilateral pleural effusions. Blood, sputum, and pleural fluid cultures were negative. Empiric antibiotics were started but the clinical course was complicated by a Coomb's positive (indirect and direct) hemolytic anemia and thrombocytopenia which responded to oral Prednisone therapy. Oral herpetic lesions also developed and were treated successfully with oral Acyclovir. Shortly after the discontinuation of Prednisone, the patient became febrile with declining neutrophil counts and developed a syndrome of inappropriate ADH secretion which responded to fluid restriction. However, at the request of both patient and family, all active treatment was withdrawn and the patient died 24 h later. At autopsy, death was attributed to cardiorespiratory failure secondary to right ventricular thrombus, myocarditis, and probable septicemia.

Patient II-3

In October 1985, II-3, the 35-year-old brother of the propositus, was found to have isolated thrombocytopenia. Hb was 131 g/L, ANC 2.4×10^9/L, and platelets 60×10^9/L. Coomb's and Ham's tests were negative, and all other biochemistry was within normal limits. He had no organomegaly or lymphadenopathy and no previous history of chemotherapy or chemical exposure. The patient had been on antihypertensive medication which was discontinued 3 months prior to presentation. He was a lifetime nonsmoker.

Bone marrow aspirate was hypocellular with regard to marrow particles. Erythropoiesis was normoblastic, and the myeloid series was normal. Only one to two megakaryocytes were seen in a biopsy specimen with a hypocellular and fatty marrow. No cytogenic studies were performed at this time.

Four months after presentation a repeat bone marrow biopsy revealed a normocellular marrow with adequate hemosiderin. Oral Prednisone was initiated with no rise in platelet count; platelet-associated IgG levels were normal. The androgen Fluoxymesterone was started at which time Hb was 135 g/L, ANC 1.8×10^9/L, and platelets 56×10^9/L. Vitamin B_{12} and folate levels were normal. The platelet count stabilized temporarily on Fluoxymesterone with both Hb and white cell counts remaining normal. However, the platelet count gradually declined and, by September 1987, had dropped to 41×10^9/L. Hb was 131 g/L, ANC 1.6×10^9/L, and MCV was elevated at 107.5 fL. Vitamin B_{12} and folate levels remained normal. Fluoxymesterone was subsequently discontinued. A bone marrow aspirate at this time was normocellular to slightly hypocellular. A few megaloblastoid cells were observed though myelopoiesis was unremarkable. There were sparse megakaryocytes. With the marked abnormalities in red cell morphology (moderate to marked anisocytosis with moderate poikilocytosis), subtle dyserythropoiesis, and ongoing thrombocytopenia, a diagnosis of unspecified MDS was made.

Over the ensuing months, in the absence of drug therapy, the patient's hemoglobin gradually dropped and by May 1988 was 126 g/L; platelet count was 43×10^9/L; and ANC, 1.0×10^9/L. A bone marrow aspirate in No-

vember 1988 was insufficient for diagnosis but did reveal a myeloid/erythroid ratio of 4:1, orderly maturation of both cell lines, and no megaloblastic changes. Stainable iron was present, and no ringed sideroblasts were observed. Cytogenetics performed at this time showed a normal karyotype.

By July 1989 the patient had evidence of pancytopenia with Hb 111 g/L, ANC 1.6 × 10^9/L, and platelets 35 × 10^9/L. His bone marrow studies continued to show a hypocellular specimen. Repeat cytogenetic studies were unremarkable. He was started on oral Danazol therapy which stabilized his hemoglobin and helped maintain his platelet counts at about 50 × 10^9/L.

In April 1992, while on Danazol therapy, the patient's Hb was 148 g/L, white cell count 4.2 × 10^9/L, and platelet count 51 × 10^9/L, with normal differential count. A bone marrow aspirate was normocellular but cellularity was difficult to assess. Erythroid precursors were normoblastic with the myeloid series showing no maturation arrest. Megakaryocytes, although difficult to find, were present and had a smooth contour. Cytogenetics showed that 50% of the cells examined had a derivative chromosome 7 (46,XY,der(7)t(1;7)(q21;q11)[10]/46,XY[10]), resulting in trisomy for 1q and monosomy for 7q. These findings are compatible with a myeloproliferative disorder or MDS.

In July 1994, while on Danazol therapy, the patient remained clinically stable; his peripheral bloodwork revealed Hb 144 g/L, ANC 1.7 × 10^9/L, and platelet count 243 × 10^9/L. Flow cytometry of both peripheral blood cells and marrow was unremarkable. However, his cytogenetic profile had deteriorated with less than half the cells showing a normal karyotype. The modal karyotype was 46,XY/46,XY der 7t(1;7)/46,XY,der 21t(1;21). Some abnormal cells showed presence of double minutes (evidence of oncogene amplification). The above karyotypic changes resulted in functional trisomy for 1q. The two cell lines are thought to represent clones with all findings compatible with MDS.

In August 1995 the patient developed a spontaneous retinal hemorrhage and associated hyphema. A gradual trilineage decrease in blood counts was observed with symptomatic anemia and mucosal bleeding. The patient was lost to follow-up after referral to a distant tertiary care centre for allogeneic bone marrow transplantation. He died of transplant complications 3 weeks post reinfusion.

Patient III-9

In January 1992, at the age of 25, III-9, the son of the propositus, was noted to be neutropenic and thrombocytopenic on routine annual blood work. Past medical history was otherwise unremarkable, and he was on no medications. His Hb was 149 g/L, ANC 1.9 × 10^9/L, and platelets 132 × 10^9/L. The remainder of his biochemistry was within normal limits. He had no organomegaly or lymphadenopathy and no previous history of chemotherapy or chemical exposure. He was a nonsmoker. An iliac crest bone marrow aspirate revealed an aparticulate specimen which was not amenable to interpretation. Bone marrow biopsy showed a markedly hypocellular marrow. Only adult-appearing fat was found within the spicules and was felt to represent total hypoplasia. Cytogenetic analysis of the marrow could not be performed due to the absence of metaphase cells in the specimen.

The patient remained asymptomatic with stable thrombocytopenia and neutropenia over the next 2 years. In view of the clinical presentation of both his father and uncle, a diagnosis of unclassified MDS was made.

In January 1995, a repeat bone marrow specimen was taken sternally due to repetitive "dry" taps in the iliac crest and showed a normal male karyotype. In July 1995 the patient remained clinically stable with Hb 144 g/L, ANC 1.8 × 10^9/L, and platelets 70 × 10^9/L.

In August 1998, the patient had symptomatic leukopenia and thrombocytopenia with mouth aphthous ulcerations and ease of bruising. Blood counts were decreased with ANC 1.0 × 10^9/L, Hb 90 g/L, and platelets 30 × 10^9/L. The patient was lost to follow-up after referral to a tertiary centre for allogeneic bone marrow transplantation, but reportedly had evolving chromosomal changes compatible with worsening MDS, including the presence of an extra i (1q) and monosomy 7.

Patient I-1

I-1 is the paternal uncle of the propositus. In March 1994, at the age of 69, he presented with a 3-month history of decreased exercise tolerance, ease of bruisability, and prolonged bleeding after shaving. He also reported anorexia and a 7 kg weight loss over the same time period with some left upper quadrant abdominal discomfort. There was massive splenomegaly 16 cm below the umbilicus with cervical, axillary, and groin lymphadenopathy. Scattered petechiae were noted. The patient was a longtime heavy smoker with no previous history of chemotherapy or excessive exposure to benzene or other chemicals. His Hb was 71 g/L, white cell count 150.8 × 10^9/L, lymphocytes 148.5 × 10^9/L, neutrophils 2.3 × 10^9/L, and platelets 38 × 10^9/L. Peripheral blood smear analysis was consistent with a diagnosis of chronic lymphocytic leukemia (CLL). Protein electrophoresis was essentially within normal limits with the exception of a mildly decreased gamma globulin of 3 g/L. Direct Coomb's screen for polyspecific antibodies was negative. No bone marrow testing was performed at the time of diagnosis. The patient was started on oral Prednisone and Chlorambucil therapy.

Over the following several months the patient's anemia gradually improved on oral Chlorambucil as did his lymphocytosis and massive splenomegaly. He was suc-

cessful treated for minor respiratory infections with oral antibiotics as an outpatient but otherwise had no severe infections or bleeding tendencies. In October 1994 his Hb was 113 g/L, white cell count 6.6×10^9/L, lymphocytes 2.6×10^9/L, neutrophils 3.7×10^9/L, and platelets 122×10^9/L.

Although bone marrow and cytogenetic testing was not clinically indicated, the patient kindly consented to these investigations for the purposes of this study. Bone marrow aspirate was cellular with a myeloid/erythroid ratio of approximately 1:1. Myeloid maturation was unremarkable. Erythroid maturation was mostly unremarkable with occasional dysplastic and megaloblastic forms. Megakaryocytes were normal. Lymphocytes were at 43% with mostly small round forms and few intermediate-sized cells. There was increased stainable iron with an occasional sideroblast although no ringed sideroblasts were observed. Biopsy revealed myeloid and erythroid elements with an erythroid predominance and scattered lymphoid nodules in a non-paratrabecular location. Neither bone marrow biopsy nor aspirate revealed overt myelodysplasia. Cytogenetic analysis showed a normal male karyotype with no evidence of abnormal cell lines.

In June 1995 the patient was clinically stable on oral Chlorambucil with Hb 144 g/L, white cell count 6.0×10^9/L, and platelets 126×10^9/L.

By February 1997, the patient had gradually worsening anemia and leukocytosis despite increases in oral Chlorambucil. Due to his advanced age, he declined further treatment and died of sepsis complications.

Other Family Members

The propositus' father died at age 73 with the cause of death attributed to cardiovascular disease. No other details are available.

The propositus and patient II-3 have two other siblings, who, along with their children, have no evidence of blood or autoimmune disorders. The 22-year-old daughter of the propositus is clinically well but has declined bloodwork for this study. Two grandchildren of the propositus, children of his 32-year-old daughter, are also clinically well but their bloodwork status is also unknown.

DISCUSSION

We have described MDS in three family members, in two generations, with age of onset before 55. A fourth individual in a third generation was diagnosed with CLL. Both early age of onset and a familial tendency with no common exposure to potential carcinogens are rare features of MDS.

In a large population study over 10 years, Williamson et al. [19] found the age-specific incidence of MDS per 100,000 for age less than 50 years was only 0.5 and for age 50–59 years, 5.3. Rates per 100,000 for individuals age 60–69, 70–79, and 80+ years were 15, 49, and 89, respectively. De novo MDS in adults age 50 or less has been described elsewhere [18], however, the familial cases were not closely examined and many of the patients had previous exposure to potential carcinogens. In contrast, we found no evidence for common exposure to chemical agents in our patients. Since the propositus worked as a motor vehicle technician for over 30 years, it is of interest that exposure to gasoline fumes or ammonia are known risk factors for MDS [20]. However, neither his son (III-9) nor his brother (II-3) had a similar exposure history. Patient III-9 had worked as a computer assembly technician, while patient II-3 had been employed in various manual labor occupations with no unusual exposure history.

Mineishi et al. [21] have described a type of "hypoplastic MDS" characterized by hypoplastic marrow with dysplasia (marrow cellularity under 40%) rather than the normocellular or hypercellular marrow as dictated by strict FAB/MDS-definition criteria. These patients also present with pancytopenia, persistent anemia, or thrombocytopenia and have dysplastic features in one or more cell lineages on marrow biopsy or aspirate and/or cytogenetic abnormalities. In the present study, both patients II-3 and III-9 have had hypoplastic marrow aspirates or biopsies and peripheral blood findings in keeping with this syndrome. Whereas patient II-3 showed both cytogenetic abnormalities and dysplasia upon bone marrow biopsy, patient III-9 showed only evolving chromosomal changes without evidence of dysplasia. In addition, hypoplastic MDS patients frequently present with "dry" iliac crest bone marrow aspirates whereas sternal sampling is more successful (personal communication, Mineishi 1994). Such a pattern was observed with patient III-9 and to a lesser extent with patient II-3. Hypoplastic MDS patients achieve good longterm survival after allogeneic BMT or, alternatively, respond to immunosuppressive therapy with antithymocyte globulin (ATG) if no HLA-matched relative is available [21]. Patient II-3 and, to a lesser extent, III-9 have clinical pictures consistent with a diagnosis of hypoplastic MDS. However, Tuzuner et al. [22] showed that correction of cellularity using age-adjusted normal marrow biopsies resulted in few MDS patients being diagnosed with true hypocellularity. This correction may affect the diagnosis of hypoplastic MDS.

Previous studies of familial MDS [6,7] revealed various cytogenetic abnormalities but none of these was found to be consistently associated with the disease. In our study, monosomy 7 was noted in the propositus and functional monosomy 7, resulting from a balanced translocation, in patient II-3. Abnormalities of chromosome 7 have been frequently associated with familial MDS and leukemia in the literature. Familial monosomy 7 syn-

drome has been characterized [23], but these patients are often children and monosomy 7 is the only demonstrable cytogenetic abnormality. Brodeur et al. [24] and Shannon et al. [25] have reported an increased incidence of monosomy 7 and juvenile chronic myelogenous leukemia (JCML) in children with neurofibromatosis type 1, suggesting a multistep mechanism of malignant transformation with a common molecular basis for both. The fact that all of the affected individuals in this family are male is of particular interest given the findings of Shannon et al. [25] which show a marked predilection for JCML and monosomy 7 in boys. On the other hand, the family showed clear male to male transmission, while Shannon's cases did not.

Both the propositus and patient II-3 had multiple chromosomal changes. The most recent cytogenetic findings pertaining to patient II-3 have revealed the presence of double minutes, suggesting oncogene amplification.

Although age of onset and clinical course have differed among our patients, the familial nature of the disease along with the absence of a common exposure history raise the possibility of an inherited abnormality. Although the affected members are all male the putative pattern of inheritance would appear to be autosomal and not X-linked. This is similar to the inheritance pattern observed by Marsden et al. [4] in families with late-onset MDS. In the present study, variable age of onset of disease (25, 35, and 52 years) suggests a possible predisposing genetic abnormality which requires additional changes for the disease to become manifest. The presence of comparatively mild cytogenetic abnormalities in patient III-9, progressive abnormalities in patient II-3 and gross changes in the propositus, may reflect a continuum of disease in which the development of chromosomal abnormalities mirrors clinical disease progression. Detailed studies of family members at the molecular level are in progress to further elucidate possible mechanisms of pathogenesis in MDS.

The variability in age of onset of MDS in our pedigree is also consistent with anticipation, a phenomenon characterized by increased severity of disease and/or earlier age of onset with each successive generation. Anticipation resulting from trinucleotide expansion within the coding region or regulatory elements of the causative gene is well documented in neurological disorders such as Fragile X syndrome [26] and Huntington's disease [27]. Recently, Horowitz et al. [28] have also reported evidence of anticipation in familial leukemia, including AML, and suggest that an unstable trinucleotide repeat mutation may play a role in some inherited hematopoietic malignancies.

Patient I-1, the paternal uncle of the propositus, was diagnosed with CLL at age 69. CLL is not classically associated with abnormalities in the myeloid series of cells. However, CLL with concomitant MDS, i.e., two separate clonal cell populations, has been observed (personal communication, Dewald 1994). MDS also occurs simultaneously with other hematologic conditions including aplastic anemia, hemoglobin H disease and paroxysmal nocturnal hemoglobinuria [29–32]. Although patient I-1 showed no cytogenetic abnormalities, marrow examination revealed possible early dysplastic changes. Although these findings may be treatment-related and are based on unilineage erythroid hyperplasia, they are noteworthy especially in view of the family history of MDS.

In summary, we have described three cases of de novo MDS with an early age of onset and one case of CLL in a three generation pedigree, suggesting a genetic predisposition to the development of MDS. Ongoing studies at the molecular level may help elucidate the pathogenesis of MDS and shed some light on the mechanisms underlying leukemogenesis.

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